



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: FEB 25 2004
From: Division of Dietary Supplement Programs, Office of Nutritional Products,
Labeling and Dietary Supplements, HFS-810
Subject: 75-Day Pre-market Notification of New Dietary Ingredients
To: Dockets Management Branch, HFA-305

Subject of the Notification: Carnitine Creatinate Monohydrate

Firm: AMT Labs, Inc.

Date Received by FDA: August 13, 2003

90-Day Date: November 12, 2003

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day pre-market notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Attachments

95S-0316

RPT208



OCT 22 2003

Mr. Oliver L. Fang
AMT Labs, Inc.
536 North 700 West
North Salt Lake, UT 84054

Dear Mr. Fang:

This is to inform you that the notification, dated August 6, 2003, you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on August 13, 2003. Your notification concerns the substance "Carnitine Creatinate Monohydrate" that you intend to market as a new dietary ingredient.

The notification informs FDA that AMT Labs, Inc. intends to market the new dietary ingredient, "Carnitine Creatinate Monohydrate", in powder, tablet, or capsule form. The notification states that the recommended daily dose is up to 3.8 grams a day. Your notification states: "L-Carnitine should be used by pregnant women only if clearly indicated and only under medical supervision. It is not advised for nursing mothers. Those with seizure disorders should take L-Carnitine only under medical supervision and advisement." The notification also states, "It may be prudent for those with impaired renal function and renal disorders such as nephrotic syndrome to avoid creatine."

Under 21 U.S.C. 350b(a)(2), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

According to your notification, "Carnitine Creatinate Monohydrate" is a salt of carnitine and creatinate monohydrate. However it is unclear whether "Carnitine Creatinate Monohydrate" is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1) that may be lawfully used in dietary supplements. The term "dietary supplement" is defined in 21 U.S.C. 321(ff). A dietary supplement means, among other things, a "product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."

Based on the information in your submission, it is unclear that "Carnitine Creatinate Monohydrate" is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1). Therefore, notwithstanding the discussion below of the evidence you rely upon as evidence that your products are reasonably expected to be safe, FDA cannot determine, at this time, whether your product contains a dietary ingredient that may lawfully be marketed as a dietary supplement.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing "Carnitine Creatinate Monohydrate" when used under the conditions recommended or suggested, will reasonably be expected to be safe. Your notification does not contain any information that specifically addresses the safety of consumption of the salt, carnitine creatinate monohydrate. In addition, the notification fails to identify the carnitine isomer present in the salt (i.e., whether the carnitine is D or L carnitine or a racemic mixture of the two). Moreover, a copy of patent number 5,994,581 was not included in the notification.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "Carnitine Creatinate Monohydrate", when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of August 6, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

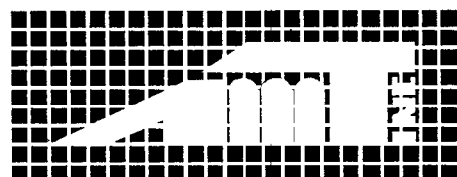
If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-1775.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Susan Walker", with a stylized flourish at the end.

Susan J. Walker, M.D.
Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

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AMT Labs, Inc.

Memo

FDA/L.B

To: Food and Drug Administration **From:** Oliver L. Fang

Attn: **Pages:** 5

Re: Carnitine Creatinate, Monohydrate **Date:** 8/6/2003

☐ Urgent ☒ For Review ☐ Please Reply

• Comments:

Dear FDA:

I would like to submit for approval a new dietary ingredient: Carnitine Creatinate, Monohydrate (Patent Number 5,994,581).

1. Name and Complete Address:

Oliver L. Fang

Company: AMT Labs, Inc.

Address: 536 North 700 West

North Salt Lake, UT 84054

2. New Dietary Ingredient: Carnitine Creatinate, Monohydrate

3. A description of the dietary supplement:

Carnitine Creatinate, Monohydrate is a product which is the formation of a salt between carnitine and creatine. It has two constituents-carnitine and creatine. For pharmacodynamic and pharmacological considerations, it consists of the independent actions of carnitine and creatine. These components have been used widely. They are not new products. Because these two components have been used widely is our basis on which we believe our Carnitine Creatinate, Monohydrate would be a safe product to use.

85501

(Enclosed is a copy of our molecular formula for Carnitine Creatinate, Monohydrate).

Dosage:

The dosing for creatine can be a loading dose of 20 grams per day or 0.3 grams per kilogram per day in divided doses four times a day for two to five days, followed by a maintenance dose of no more than 2 grams daily or 0.03 grams per kilogram per day. (PDR for Nutritional Supplements, First Edition, Medical Economics, 2001, p. 117).

Those who take supplemental L-Carnitine for cardiovascular health (and most other possible indications) take 500 milligrams to 2 grams daily. (PDR for Nutritional Supplements, First Edition, Medical Economics, 2001, p. 259).

We recommend that people take our Carnitine Creatinate at a dose of up to 3.8 grams a day. It consists of 51.9% carnitine and 48.1% creatine monohydrate (equivalent). We get 3.8 grams a day of carnitine creatinate per day as a dosage as we take 2 grams of L-Carnitine a day divided by 0.519 as the dosage for the carnitine portion. (The amount of dosage here is determined by the carnitine portion).

The ordinary condition of use is as a powder, tablet, or capsule for nutritional supplementation.

Carnitine:

L-Carnitine is present in the foods we eat-meat and dairy products are major dietary sources of carnitine. L-Carnitine is found in nearly all cells of the body. It transports long-chain fatty acids across the inner mitochondrial membranes in mitochondria.

L-Carnitine is synthesized in the human body, mainly from the liver and kidneys from L-lysine and L-methionine. L-Carnitine is described as a conditionally essential nutrient.

L-Carnitine is already available. Oral L-Carnitine and Acetyl-L-Carnitine are available as nutritional supplements. Intravenous L-Carnitine can be utilized as a prescription orphan drug for the treatment of L-Carnitine deficiencies.

Reproductive studies performed in rats and rabbits at up to 3.8 times the human doses used for the treatment of primary and secondary L-Carnitine deficiency (on the basis of surface area) have revealed no evidence of impaired fertility or harm to the fetus due to L-Carnitine. (However, there have been no adequate and well-controlled studies in pregnant women). (PDR for Nutritional Supplements, First Edition, Medical Economics, 2001, p. 258).

Standard assays for mutagenicity indicate that L-Carnitine is not mutagenic. While mild gastrointestinal symptoms have been reported in those taking oral L-Carnitine, supplemental L-Carnitine is generally well tolerated.

To be complete, seizures have been reported to occur in those with or without pre-existing seizure disorders receiving L-Carnitine, but the incidence is low. There have been no reports of toxicity from L-Carnitine overdosage. The oral LD50 of L-Carnitine in mice is 19.2 grams per kilogram. (PDR for Nutritional Supplements, First Edition, Medical Economics, 2001, p. 258). To be careful, L-Carnitine should be used by pregnant women only if clearly indicated and only under medical supervision. It is not advised for nursing mothers. Those with seizure disorders should take L-Carnitine only under medical supervision and advisement.

(Enclosed in this information packet is a copy of the monograph for L-Carnitine from the PDR for Nutritional Supplements, First Edition, Medical Economics, 2001.

In addition, there is a product called L-Carnitine L-Tartrate (LCLT) (L-Carnipure) which has L-Carnitine as one of its components. A study was done to investigate the effects of ingesting this product on alterations in a complete blood cell profile and in circulating metabolic enzymes. The results of the study suggested that LCLT, when used as a dietary supplement, has no adverse effects on metabolic and hematological safety variables in normally healthy men. (Safety Measures of L-Carnitine L-Tartrate Supplementation in Healthy Men, Journal of Strength and Conditioning Research, 2001, 15(4), 486-490). (A copy of this citation is enclosed).

Thus, we believe that the facts that L-Carnitine is synthesized by the human body, that it is found in the foods we eat, that it has already been on the market as a nutritional supplement, that L-Carnitine L-Tartrate had no adverse effects on metabolic and hematological safety variables in normally healthy men, and that it is not mutagenic indicate that it is a safe component for use (outside of the population subsets listed above) in our product Carnitine Creatinate.

Creatine:

Creatine is a non-protein amino acid. It is produced in the body in the kidney, liver and pancreas from L-arginine, glycine, and L-methionine. Creatine has been widely available as a nutritional supplement for some time.

Creatine is used by professional athletes, college athletes, and recreational athletes. Increased ingested creatine leads to increased creatine in muscle, which may allow larger stores of phosphocreatine to build and provide more energy in the form of adenosine triphosphate.

(The following information is referenced from Creatine: A Review of Efficacy and Safety, J Am Pharm Assoc 39 (6): 803-810, 1999). (A copy of this citation is enclosed). Anecdotal reports have linked creatine use with cramping, dehydration, diarrhea, and dizziness. The Association of Professional Team Physicians has cautioned that creatine may cause dehydration and heat-related illnesses, reduced blood volume, and electrolyte imbalance. However,

creatine appears to be well tolerated judging from short-term clinical trials performed. Clinical trials noted no adverse effects, though many trials showed increased body mass. There have been two cases involving renal dysfunction and creatine use. The April 25, 1998 issue of *Lancet* had a case of a patient who was receiving cyclosporine for a condition who also used creatine. Renal function returned to baseline after creatine supplementation was discontinued. (*Lancet* 1998; 351: 1252-3) (A copy of this article is enclosed). Another report described interstitial nephritis in a 20-year-old man using creatine who was previously healthy. (Koshy KM, Griswold E, Schneeberger EE. Interstitial Nephritis in a Patient Taking Creatine. *N Engl J Med*. 1999; 340:814-815.). (A copy of the article is enclosed). Eventually, the patient's laboratory values and symptoms normalized. It may be prudent for those with impaired renal function and renal disorders such as nephrotic syndrome to avoid creatine.

D.A. Sewell, et. al. : The Effect of Acute Dietary Creatine Supplementation upon Indices of Renal, Hepatic, and Haematological Function in Human Subjects; *Proc Nutr Soc* 1998; 57: 17A concluded that acute creatine supplementation (4 x 5 g/d for 5 d) poses no obvious health risk to healthy young adults. (A copy of this document is enclosed)

R. Kreider et. al.: Long-Term Creatine Supplementation Does Not Adversely Affect Clinical Markers of Health; *Medicine and Science in Sports and Exercise* (ACSM ann. meeting abstr.) 32: S134, 2000 found that one year of monitored creatine supplementation does not adversely affect markers of health status in comparison to athletes undergoing similar training. (A copy of this abstract is enclosed).

Poortmans J.R. and Francaux M.: Long term Oral Creatine Supplementation Does not Impair Renal Function in Healthy Athletes, *Med Sci Sport Exerc* 31, 1108-1110, 1999 found that neither short-term, medium-term, nor long-term oral creatine supplements induce detrimental effects on the kidney of healthy individuals. (A copy of this article is enclosed).

Creatine should be avoided by nursing mothers, pregnant women, adolescents, and children, and those at risk for renal disorders such as diabetics. (*PDR for Nutritional Supplements*, First Edition, Medical Economics, 2001, p. 117). Three American college wrestlers died; there was a question of a link to the use of creatine supplements. However, later the deaths were found to be caused by severe dehydration and renal failure and not due to creatine. Other adverse effects are gastrointestinal (nausea, diarrhea, indigestion), muscle cramping, and strains (*PDR for Nutritional Supplements*, First Edition, Medical Economics, 2001, p. 117). (A copy of this reference is enclosed).

August 6, 2003

However, a review article in the American College of Sports Medicine has found that, in relation to muscle cramps/strains/damage there is no definitive evidence from controlled studies that implicates creatine supplementation in muscle dysfunction and/or complications in healthy individuals and/or patients with neuromuscular disease (ACSM Journal, Medicine and Science in Sports and Exercise, M.H. Williams et. al.: The Physiological and Health Effects of Oral Creatine Supplementation (March 2000, Vol. 32, No. 3).

Thus, we believe that creatine is safe for use (outside of the population subsets listed above). It is a product normally produced in the human body. It has already been used by many athletes: professional and recreational. Acute and longer studies have shown it is safe for use by healthy individuals. (Outside of the population subsets mentioned above).

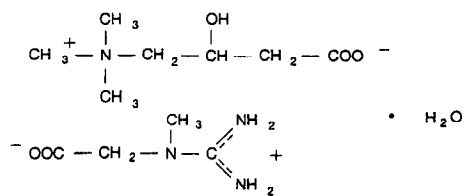
Sincerely,

 M.D.
OLIVER L. FANG M.D.

Carnitine Creatinate, Monohydrate

Patent Number: 5,994,581

Formula:



$\text{C}_{11}\text{H}_{24}\text{O}_5\text{N}_4 \cdot \text{H}_2\text{O}$
Molecular Weight=310.35